Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 49, No. 23, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.01.092

Efficacy and Safety of Enoxaparin Versus Unfractionated Heparin in Patients With ST-Segment Elevation Myocardial Infarction Also Treated With Clopidogrel

Marc S. Sabatine, MD, MPH, FACC,* David A. Morrow, MD, MPH, FACC,* Anthony Dalby, MD,† Mathias Pfisterer, MD,‡ Tibor Duris, MD,§ Jose Lopez-Sendon, MD, FACC,‖ Sabina A. Murphy, MPH,* Runlin Gao, MD, FACC,¶ Elliott M. Antman, MD, FACC,* Eugene Braunwald, MD, MACC,* for the ExTRACT-TIMI 25 Investigators

Boston, Massachusetts; Johannesburg, South Africa; Basel, Switzerland; Nove Zamky, Slovakia; Madrid, Spain; and Beijing, China

Objectives The purpose of this study was to determine the efficacy and safety of enoxaparin (ENOX) versus unfractionated heparin (UFH) in patients with ST-segment elevation myocardial infarction (STEMI) receiving fibrinolytic therapy with and without clopidogrel.

Background The efficacy and safety of ENOX and clopidogrel given together in STEMI remains to be defined.

Methods We compared the rates of major adverse cardiovascular events (MACE) as well as the rates of bleeding in medically managed patients randomized to ENOX versus UFH in the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial, stratified by concomitant clopidogrel use.

Results Enoxaparin significantly reduced the rate of the composite of death, recurrent myocardial infarction, myocardial ischemia, or stroke, compared with UFH, both in patients (n = 2,173) treated with clopidogrel (10.8% vs. 13.9%, adjusted odds ratio [OR_{adj}] 0.70, p = 0.013) and in patients (n = 12,918) not treated with clopidogrel (13.3% vs. 15.3%, OR_{adj} 0.85, p = 0.003) with no evidence of heterogeneity ($p_{interaction}$ = 0.21). The excess risk of TIMI major bleeding with ENOX versus UFH was numerically but not statistically significantly higher in patients treated with clopidogrel (2.7% vs. 1.0%) versus those who were not (2.1% vs. 1.2%) ($p_{interaction}$ = 0.61). Net clinical benefit (MACE and major bleeding) favored treatment with ENOX over UFH, either with concomitant clopidogrel (absolute risk reduction 2.4%, 95% confidence interval [CI] −0.5% to 5.3%) or without (absolute risk reduction 1.7%, 95% CI 0.5% to 3.0%) ($p_{interaction}$ = 0.61).

Conclusions In patients with STEMI receiving fibrinolytic therapy, the net benefit of ENOX is similar in patients who are and are not treated with clopidogrel. The totality of trial data suggest that the combination of a fibrinolytic, aspirin, clopidogrel, and ENOX offers an attractive pharmacologic reperfusion strategy in STEMI. (J Am Coll Cardiol 2007;49:2256–63) © 2007 by the American College of Cardiology Foundation

Adjuvant antithrombin and antiplatelet therapies play a critical role in the pharmacologic reperfusion of patients presenting with an ST-segment elevation myocardial infarction (STEMI) (1). Unfractionated heparin (UFH) has been the traditional antithrombin used (1), but it has several well-documented pharmacologic and practical limitations (2). We have

From the *Thrombolysis In Myocardial Infarction (TIMI) Study Group, Cardiovascular Division, Brigham and Women's Hospital and Department of Medicine, Harvard Medical School, Boston, Massachusetts; †South African Cardiology Clinical Trials Group, Milpark Hospital, Johannesburg, South Africa; ‡Kantonsspital, Basel, Switzerland; §FNsP, Nove Zamky, Slovakia; ‖Hospital Universitario La Paz, Madrid, Spain; and ¶Fu Wai Hospital, Beijing, China. The ExTRACT-TIMI 25 study was supported by a research grant from Sanofi-Aventis to the TIMI Study Group. All authors have received research grant support from Sanofi-Aventis. In addition, Dr. Sabatine has received research grant support from Bristol-Myers Squibb, and has received honoraria from and consulted for Bristol-Myers Squibb, Daiichi-Sankyo, and Sanofi-Aventis. Dr. Morrow has received honoraria from and consulted for Sanofi-Aventis. Dr. Lopez-Sendon has received research grants from Bristol-Myers Squibb, Servier, Pfizer, and Cardiovascular Therapeutics; honoraria from Sanofi-Aventis; and has consulted for Servier. Drs. Antman and Braunwald have received honoraria from Sanofi-Aventis. The TIMI Study Group received research grant support from: Accumetrics, Amgen, AstraZeneca, Bayer Healthcare, Beckman Coulter, Biosite, Bristol-Myers Squibb, CV Therapeutics, Eli Lilly and Company, GlaxoSmithKline, Inotek Pharmaceuticals, Integrated Therapeutics, Merck & Co., Millennium Pharmaceuticals, Novartis Pharmaceuticals, Nuvelo, Ortho-Clinical Diagnostics, Pfizer, Roche Diagnostics, Sanofi-Aventis, and Schering-Plough Research Institute.

Manuscript received September 7, 2006; revised manuscript received December 21, 2006, accepted January 2, 2007.

shown in the ExTRACT-TIMI 25 (Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment–Thrombolysis In Myocardial Infarction 25) trial that a strategy of the low-molecular-weight heparin (LMWH) enoxaparin (ENOX) was superior to a strategy of UFH in preventing death or recurrent ischemic events in patients receiving fibrinolytic therapy for STEMI (3). While the ExTRACT-TIMI 25 trial was enrolling subjects, 2 trials of another adjuvant therapy in STEMI, clopidogrel, were completed. Specifically, both the CLARITY (Clopidogrel as Adjunctive Reperfusion Therapy)-TIMI 28 study (4) and COMMIT/CCS-2 study (Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study) (5) demonstrated that the addition of clopidogrel to a standard reperfusion regimen including aspirin reduced the rate of both death and recurrent ischemic events. With these 2 recent observations, the question arose as to whether clopidogrel and ENOX can and should be used together. Each drug significantly reduces major adverse cardiovascular events (MACE) in STEMI; however, whether those benefits would be additive or redundant remains to be defined. Similarly, in terms of safety, ENOX was associated with a modest but statistically significant increase in major bleeding in the ExTRACT-TIMI 25 trial (3), and clopidogrel was associated with an increase in minor bleeding in the COMMIT/CCS-2 trial (5); such an increase in bleeding with clopidogrel was not seen in the CLARITY-TIMI 28 trial (4), which did not enroll patients >75 years of age. Neither clopidogrel nor ENOX was associated with an excess of intracranial hemorrhage (ICH) when each drug was analyzed in isolation. To evaluate the impact of combining ENOX and clopidogrel, we analyzed the efficacy and safety profile of ENOX compared with UFH in medically-treated patients who did and did not receive concomitant clopidogrel in the ExTRACT-TIMI 25 trial.

Abbreviations and Acronyms

ENOX = enoxaparin
ICH = intracranial hemorrhage
LMWH = low-molecular-weight heparin
MACE = major adverse cardiovascular event
MI = myocardial infarction
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction
UFH = unfractionated heparin

Methods

Patient population and procedures. The design of the ExTRACT-TIMI 25 trial has been reported (6). In brief, the intention-to-treat cohort consisted of 20,479 patients

Table 1 Baseline Characteristics by Clopidogrel Use

Variable	Clopidogrel (n = 2,173)	No Clopidogrel (n = 12,918)	p Value
Baseline characteristics			
Age, yrs	58 ± 12	61 ± 12	<0.001
Age ≥75 yrs	211 (9.7)	1,848 (14.3)	<0.001
Male	1,737 (79.9)	9,555 (74.0)	<0.001
Caucasian	1,325 (61.0)	12,107 (93.7)	<0.001
Weight, kg	74 ± 15	78 ± 14	<0.001
Hypertension	881 (41.0)	5,964 (46.8)	<0.001
Hyperlipidemia	303 (18.5)	1,504 (15.9)	0.008
Current smoker	1,022 (47.1)	5,976 (46.3)	0.51
Diabetes mellitus	398 (18.5)	1,793 (14.1)	<0.001
Prior MI	258 (11.9)	1,763 (13.7)	0.025
Prior angina pectoris	520 (24.1)	3,983 (31.0)	<0.001
Prior PCI	91 (4.2)	234 (1.8)	<0.001
Index presentation and medications			
Anterior MI	971 (45.1)	5,765 (45.0)	0.94
SBP, mm Hg	133 ± 21	134 ± 20	0.10
Heart rate, beats/min	77 ± 16	77 ± 17	0.50
Killip class II to IV	239 (11.0)	1,568 (12.1)	0.13
Creatinine clearance, ml/min	80 (62–101)	80 (62–104)	0.22
Time from symptom onset to start of fibrinolytic, h	3.3 ± 1.8	3.4 ± 1.4	0.13
Fibrin-specific lytic	1,759 (81.0)	10,309 (79.8)	0.22
Randomized allocation to ENOX	1,083 (49.8)	6,528 (50.5)	0.55
Beta-blocker	1,833 (84.4)	11,111 (86.0)	0.04
ACE inhibitor or ARB	1,771 (81.5)	10,240 (79.3)	0.02
Statin	1,757 (80.9)	7,969 (61.7)	<0.001

Data are presented as mean ± SD for continuous variables, median (interquartile range) for non-normally distributed continuous variables, and n (%) for dichotomous variables. Denominators are based on available data for each characteristic.

ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; ENOX = enoxaparin; MI = myocardial infarction; PCI = percutaneous coronary intervention; SBP = systolic blood pressure.

JACC Vol. 49, No. 23, 2007
June 12, 2007:2256–63

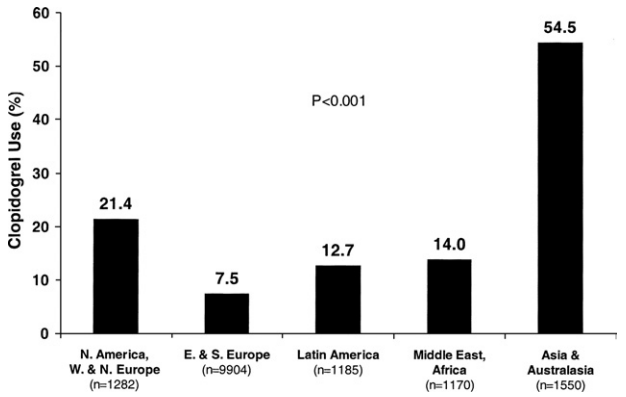

Figure 1 **Proportion of Patients Receiving Clopidogrel in Different Geographic Regions**

Regions are based on the United Nations Statistics Geographic Region Codes. North America and Western and Northern Europe includes Austria, Belgium, Canada, Estonia, Finland, France, Germany, Ireland, Latvia, Lithuania, the Netherlands, Norway, Sweden, Switzerland, United Kingdom, and the U.S. Eastern and Southern Europe includes Belarus, Bulgaria, Croatia, Greece, Hungary, Italy, Poland, Portugal, Romania, Russia, Slovakia, Spain, and Ukraine. Latin America includes Argentina, Brazil, Chile, Mexico, and Uruguay. Middle East and Africa includes Israel, Jordan, Lebanon, South Africa, and Turkey. Asia and Australasia includes Australia, China, Hong Kong, India, Republic of Korea, Malaysia, New Zealand, Singapore, and Thailand. $p < 0.001$ for global chi-square as well as for all pairwise comparisons except for the rates in Latin America versus the Middle East and Africa.

at least 18 years of age presenting within 6 h of onset of STEMI and scheduled to undergo fibrinolysis who were randomized to receive ENOX or UFH. Patients with contraindications to fibrinolytic therapy, cardiogenic shock, or renal insufficiency (serum creatinine >2.5 mg/dl for men and >2.0 mg/dl for women) and those who had received LMWH within the prior 8 h were excluded. The study protocol was approved by the relevant institutional review boards, and informed consent was obtained from all patients.

Study medication was administered in a double-blind fashion with a double-dummy design. The doses and regimens of ENOX and UFH employed have been described in detail (3,6). For this analysis, patients who did not receive a fibrinolytic or did not receive aspirin at presentation were excluded. Clopidogrel could be given at the discretion of the treating physician. Patients were classified as having received clopidogrel if they were given clopidogrel during study drug administration. To study patients who received clopidogrel as part of their medical, pharmacologic reperfusion therapy, for the primary analysis in this substudy we excluded patients who underwent percutaneous coronary intervention (PCI). However, a further safety analysis was performed in which we analyzed the rates of bleeding in patients who did undergo PCI during the index hospital stay.

Outcomes. Efficacy outcomes included the composite of death, nonfatal recurrent myocardial infarction (MI), nonfatal recurrent severe myocardial ischemia (ischemic discomfort at rest ≥10 min accompanied by new, horizontal, or downsloping ST-segment depression), or nonfatal stroke through 30 days as well as the individual components (6). Safety outcomes included TIMI major bleeding (fatal or nonfatal) (7), ICH (fatal or nonfatal), and TIMI minor bleeding through 30 days. Events were adjudicated by an independent clinical events committee that was blinded to treatment assignment.

Statistical analysis. The characteristics of patients who were and were not treated by their physician with clopidogrel as well as of those who were randomized to ENOX versus UFH within each clopidogrel use subgroup were compared with *t* tests for continuous variables, Wilson rank sum tests for non-normally distributed continuous variables, and chi-square tests for categorical variables. Adjusted odds ratios (OR_{adj}) and 95% confidence intervals (CIs) were calculated in multivariable logistic regression models that adjusted for the components of the TIMI risk score for STEMI (age, diabetes mellitus, hypertension, previous angina, systolic blood pressure, heart rate, Killip class, weight, anterior MI, left bundle branch block, and time to fibrinolytic therapy) (8) to quantify the unconfounded effect of ENOX versus UFH on the incidence of the efficacy and safety outcomes; analyses were conducted separately in patients who were and were not were treated with clopidogrel. Per the main trial's statistical analysis plan, efficacy analyses were performed in the intent-to-treat population and safety analyses were performed in the as-treated population. Tests for interaction between clopidogrel, study

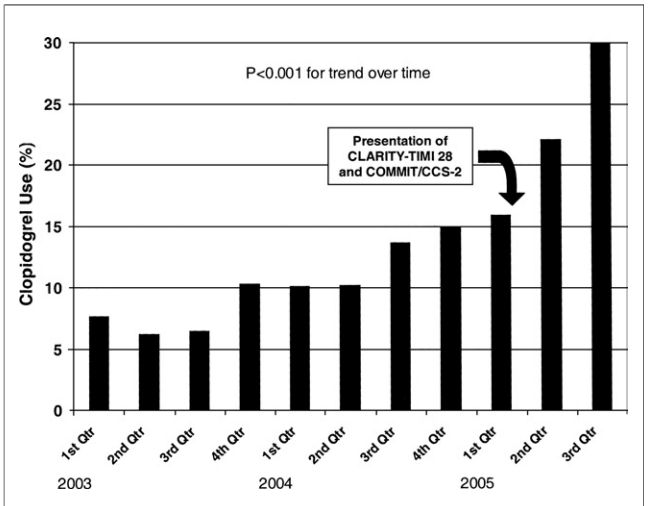

Figure 2 **Proportion of Patients Receiving Clopidogrel as a Function of Date of Enrollment**

The first quarter of 2003 also includes a small number of patients (n = 42) enrolled in the last quarter of 2002 (when the trial started enrollment), and the third quarter of 2005 also includes a small number of patients (n = 7) enrolled in the fourth quarter of 2005 (when the trial completed enrollment). CLARITY-TIMI 28 = Clopidogrel as Adjunctive Reperfusion Therapy–Thrombolysis in Myocardial Infarction 28 trial; COMMIT/CCS-2 = Clopidogrel and Metoprolol in Myocardial Infarction Trial/Second Chinese Cardiac Study.

Table 2 Baseline Characteristics by Treatment Group Within Clopidogrel Cohorts

Variable	Clopidogrel (n = 2,173)			No Clopidogrel (n = 12,918)		
	ENOX (n = 1,083)	UFH (n = 1,090)	p Value	ENOX (n = 6,528)	UFH (n = 6,390)	p Value
Baseline characteristics						
Age, yrs	58 ± 12	58 ± 12	0.72	61 ± 12	61 ± 12	0.05
Age ≥75 yrs	113 (10.4)	98 (9.0)	0.26	891 (13.7)	957 (15.0)	0.03
Male	856 (79.0)	881 (80.8)	0.30	4,837 (74.1)	4,718 (73.8)	0.73
Caucasian	660 (60.9)	665 (61.0)	0.97	6,108 (93.6)	5,999 (93.9)	0.48
Weight, kg	74 ± 14	75 ± 15	0.69	78 ± 15	78 ± 14	0.04
Hypertension	436 (40.9)	445 (41.1)	0.93	3,025 (46.9)	2,939 (46.6)	0.70
Hyperlipidemia	149 (18.3)	154 (18.7)	0.81	789 (16.5)	715 (15.3)	0.10
Current smoker	492 (45.4)	530 (48.7)	0.13	3,035 (46.5)	2,941 (46.1)	0.62
Diabetes mellitus	192 (17.8)	206 (19.1)	0.42	925 (14.4)	868 (13.8)	0.33
Prior MI	132 (12.3)	126 (11.6)	0.63	895 (13.8)	868 (13.6)	0.81
Prior angina pectoris	251 (23.4)	269 (24.8)	0.45	2,017 (31.1)	1,966 (30.9)	0.83
Prior PCI	43 (4.0)	48 (4.4)	0.62	129 (2.0)	105 (1.6)	0.16
Index presentation and medications						
Anterior MI	478 (44.6)	493 (45.5)	0.66	2,876 (44.4)	2,889 (45.5)	0.20
SBP, mm Hg	133 ± 21	133 ± 21	0.96	133 ± 20	134 ± 20	0.15
Heart rate, beats/min	77 ± 17	76 ± 16	0.09	77 ± 17	77 ± 16	0.51
Killip class II to IV	114 (10.5)	125 (11.5)	0.48	804 (12.3)	764 (12.0)	0.53
Creatinine clearance, ml/min	80 (61–101)	80 (63–103)	0.39	82 (63–105)	80 (62–103)	0.01
Time from symptom onset to start of fibrinolytic, h	3.3 ± 2.2	3.3 ± 1.4	0.58	3.4 ± 1.4	3.4 ± 1.4	0.78
Fibrin-specific lytic	879 (81.2)	880 (80.7)	0.80	5,207 (79.8)	5,102 (79.8)	0.91
Beta-blocker	921 (85.0)	912 (83.7)	0.38	5,626 (86.2)	5,485 (85.8)	0.57
ACE inhibitor or ARB	881 (81.4)	890 (81.7)	0.86	5,194 (79.6)	5,046 (79.0)	0.40
Statin	860 (79.4)	897 (82.3)	0.09	4,073 (62.4)	3,896 (61.0)	0.10

Data are presented as mean ± SD for continuous variables, median (interquartile range) for non-normally distributed continuous variables, and n (%) for dichotomous variables. Denominators are based on available data for each characteristic.

UFH = unfractionated heparin; other abbreviations as in Table 1.

medication, and outcomes were performed with logistic regression models that included terms for randomized treatment assignment, clopidogrel use, and randomized treatment × clopidogrel use.

Results

Among patients who received a fibrinolytic and aspirin on presentation and who did not undergo PCI during the index hospital stay, a total of 2,173 were treated with clopidogrel and 12,918 were not. The baseline characteristics of the 2 groups are shown in Table 1. Patients who received clopidogrel were younger, more likely to be male, and less likely to be Caucasian. They were also less likely to have hypertension and more likely to have hyperlipidemia or diabetes mellitus. Patients treated with clopidogrel were less likely to have prior angina pectoris or a previous MI but more likely to have had a previous PCI, although the rates of the latter were low (<5%) in both groups. There were no significant differences in the time from symptom onset to the start of fibrinolytic therapy, MI location, vital signs, Killip class, or creatinine clearance between patients who did and who did not receive clopidogrel. Randomization to ENOX and use of fibrin-specific lytics did not differ between the 2 groups. Use of beta-blockers and of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers was high (approximately 80%) in both groups. Patients who were treated with clopidogrel were more likely to receive a statin.

The proportion of patients who received clopidogrel varied by geographic region (Fig. 1), and was highest among patients enrolled in Asia and Australasia (54.5%), high in North America and Western and Northern Europe (21.4%), intermediate in Latin America (12.7%) and the Middle East and Africa (14.0%), and lowest in Eastern and Southern Europe (7.5%) ($p < 0.001$ for global chi-square as well as for all pairwise comparisons except for the rates in Latin America vs. the Middle East and Africa). Use of clopidogrel as part of the adjuvant medical therapy also increased over time (Fig. 2), starting at approximately 7.5% at the beginning of the trial and quadrupling to 30% by the end of the trial ($p < 0.001$ for trend over time). The rate of clopidogrel use nearly doubled in the 6 months after March 2005, when the results of the CLARITY-TIMI 28 and COMMIT/CCS-2 studies were presented.

As was the case in the overall trial, there were no clinically significant differences in the baseline characteristics or index presentation and treatments between patients randomized to ENOX versus UFH, in either the clopidogrel or the no clopidogrel cohorts (Table 2).

Enoxaparin significantly reduced the rate of the composite of death, recurrent MI, recurrent myocardial ischemia, or

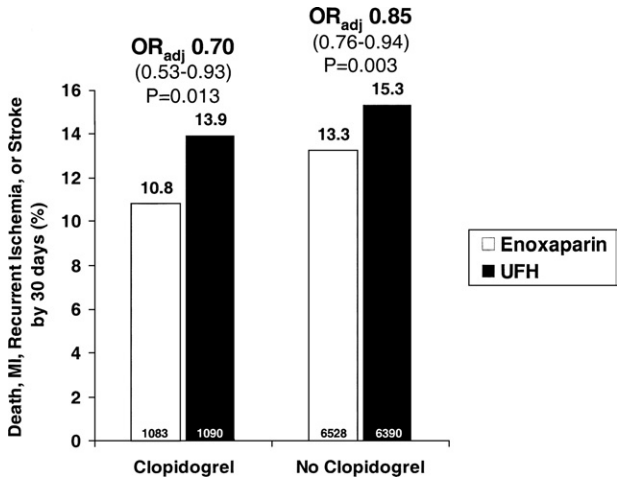

Figure 3 **Composite Efficacy Outcome Stratified by Clopidogrel Use**

Efficacy of enoxaparin over unfractionated heparin (UFH) in reducing death, myocardial infarction (MI), recurrent ischemia, or stroke stratified by clopidogrel use. OR$_{adj}$ = adjusted odds ratio.

stroke by 30 days, both in patients treated with clopidogrel (10.8% vs. 13.9%, OR$_{adj}$ 0.70, 95% CI 0.53 to 0.93, p = 0.013) and in patients not treated with clopidogrel (13.3% vs. 15.3%, OR$_{adj}$ 0.85, 95% CI 0.76 to 0.94, p = 0.003) (Fig. 3), with no evidence of heterogeneity (p$_{interaction}$ = 0.21) (Table 3).

The rates of bleeding and intracranial hemorrhage are shown in Table 4. The excess risk of TIMI major bleeding seen with ENOX compared with UFH was 1.7% in patients who were treated with clopidogrel (2.7% vs. 1.0%, OR$_{adj}$ 2.45, 95% CI 1.20 to 4.99, p = 0.01) and 0.9% in those who were not (2.1% vs. 1.2%, OR$_{adj}$ 1.92, 95% CI 1.41 to 2.61, p < 0.001), a difference that was not statistically significant (p$_{interaction}$ = 0.61). The absolute differences in TIMI minor bleeding between the ENOX and UFH arms were modest (<1%) and similar regardless of clopidogrel use. Lastly, there was no significant excess of ICH with ENOX compared with UFH in the overall trial, and this finding held true regardless of whether patients received concomitant clopidogrel (1.1% vs. 0.5%, OR$_{adj}$ 2.06, 95% CI 0.70 to 6.10) or not (1.0% vs. 0.8%, OR$_{adj}$ 1.45, 95% CI 0.96 to 2.20). All interaction terms were nonsignificant.

We conducted an additional safety sensitivity analysis in which we examined the rates of major bleeding with ENOX versus UFH in patients who received clopidogrel and did undergo PCI. There were 9 TIMI major bleeds among 1,016 patients in the ENOX arm (0.9%) versus 19 TIMI major bleeds among 1,134 patients (1.7%) in the UFH arm (p = 0.12). Among the 4,316 patients who received clopidogrel (regardless of PCI use), there was no significant excess in TIMI major bleeding with ENOX (1.8%) versus UFH (1.4%) (p = 0.35).

Examining both efficacy and safety (Fig. 4), for every 1,000 patients on clopidogrel treated with ENOX rather than UFH, we estimate 31 fewer patients would die or have a nonfatal MACE at the cost of 10 more patients having a nonfatal major bleed. Similarly, for every 1,000 patients not taking clopidogrel treated with ENOX rather than UFH, we estimate 21 fewer patients would die or have a nonfatal MACE at the cost of 4 more patients having a nonfatal major bleed. Thus, the net clinical benefit (composite of death, MI, myocardial ischemia, stroke, or major bleeding) (Table 5) similarly favored treatment with ENOX over UFH either with concomitant clopidogrel (absolute risk reduction 2.4%, 95% CI −0.5% to 5.3%) or without (absolute risk reduction 1.7%, 95% CI 0.5% to 3.0%) (p$_{interaction}$ = 0.61).

Discussion

A series of clinical trials in the late 1980s and early 1990s helped establish the combination of aspirin, UFH, and a fibrin-specific lytic as the foundation for pharmacologic reperfusion therapy for STEMI (9–11). Over the ensuing

Table 3 **Clinical Outcomes Through 30 Days**

Outcomes	Clopidogrel Use	ENOX	UFH	OR$_{adj}$ (95% CI)	p$_{interaction}$
Death, MI, myocardial ischemia, or stroke	Yes	117/1,083 (10.8)	152/1,090 (13.9)	0.70 (0.53–0.93)	0.21
	No	865/6,528 (13.3)	979/6,390 (15.3)	0.85 (0.76–0.94)	
Death or MI	Yes	79/1,083 (7.3)	85/1,090 (7.8)	0.86 (0.60–1.23)	0.68
	No	647/6,528 (9.9)	764/6,390 (12.0)	0.79 (0.70–0.90)	
Death	Yes	68/1,083 (6.3)	58/1,090 (5.3)	1.12 (0.74–1.69)	0.18
	No	533/6,528 (8.2)	607/6,390 (9.5)	0.83 (0.72–0.95)	
Nonfatal MI	Yes	11/1,083 (1.0)	27/1,090 (2.5)	0.43 (0.21–0.87)	0.18
	No	114/6,528 (1.8)	157/6,390 (2.5)	0.71 (0.55–0.91)	
Nonfatal myocardial ischemia	Yes	43/1,083 (4.0)	63/1,090 (5.8)	0.65 (0.43–0.99)	0.08
	No	218/6,528 (3.3)	228/6,390 (3.6)	0.99 (0.82–1.20)	
Nonfatal stroke	Yes	3/1,083 (0.3)	10/1,090 (0.9)	0.33 (0.09–1.24)	0.14
	No	46/6,528 (0.7)	52/6,390 (0.8)	0.94 (0.62–1.42)	

Data are presented as n/N (%).
CI = confidence interval; OR$_{adj}$ = adjusted odds ratio (see Methods) for event in patients randomized to enoxaparin versus unfractionated heparin; other abbreviations as in Tables 1 and 2.

Table 4 Safety Outcomes Through 30 Days

Outcomes	Clopidogrel Use	ENOX	UFH	OR_{adj} (95% CI)	$p_{interaction}$
In patients who did not undergo PCI					
Major bleeding (including ICH)	Yes	29/1,081 (2.7)	11/1,085 (1.0)	2.45 (1.20–4.99)	0.61
	No	137/6,512 (2.1)	79/6,369 (1.2)	1.92 (1.41–2.61)	
ICH	Yes	12/1,081 (1.1)	5/1,085 (0.5)	2.06 (0.70–6.10)	0.60
	No	68/6,512 (1.0)	49/6,369 (0.8)	1.45 (0.96–2.20)	
Minor bleeding	Yes	18/1,081 (1.7)	14/1,085 (1.3)	1.42 (0.67–2.98)	0.55
	No	160/6,512 (2.5)	102/6,369 (1.6)	1.63 (1.25–2.11)	
Major or minor bleeding	Yes	47/1,081 (4.4)	25/1,085 (2.3)	1.89 (1.13–3.16)	>0.99
	No	293/6,512 (4.5)	176/6,369 (2.8)	1.79 (1.46–2.19)	
In patients who underwent PCI					
Major bleeding (including ICH)	Yes	9/1,016 (0.9)	19/1,134 (1.7)	0.50 (0.21–1.18)	N/A
In patients regardless of PCI					
Major bleeding (including ICH)	Yes	38/2,097 (1.8)	30/2,219 (1.4)	1.28 (0.77–2.12)	N/A

Data are presented as n/N (%). Bleeding events were categorized according to the Thrombolysis In Myocardial Infarction criteria.
ICH = intracranial hemorrhage; other abbreviations as in Tables 1, 2, and 3.

years, no major improvements were made on that regimen (1). However, we demonstrated in the CLARITY-TIMI 28 trial that the addition of the $P2Y_{12}$ adenosine diphosphate (ADP) receptor blocker clopidogrel to standard fibrinolytic regimens including aspirin in patients with STEMI significantly improved the rate of infarct-related artery patency and decreased ischemic complications through 30 days (4). The benefit of clopidogrel in STEMI was also demonstrated in the COMMIT/CCS-2 study, which reported a significant mortality reduction with the use of clopidogrel in patients with acute MI receiving pharmacologic therapy (5). Low-molecular-weight heparin has been studied as an alternative antithrombin to UFH in several trials. Although the results were favorable, most trials were angiographic studies, and none was blinded (12). In contrast, the ExTRACT-TIMI 25 trial was nearly 3 times as large as all of the previous trials combined and was conducted with a double-blind, double-dummy design. The ExTRACT-TIMI 25 trial thus provided a rigorous demonstration of the superiority of a strategy of ENOX compared with a strategy of UFH in terms of preventing death or ischemic complications.

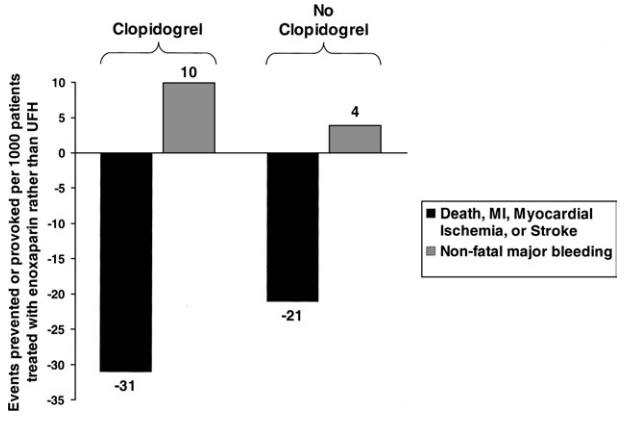

Figure 4 Events Prevented or Caused by Treatment With ENOX Rather Than UFH Stratified by Clopidogrel Use

The absolute number of events prevented (negative value) or provoked (positive value) per 1,000 patients treated with enoxaparin (ENOX) rather than unfractionated heparin (UFH). MI = myocardial infarction.

The simultaneous testing of adjuvant therapy with clopidogrel and ENOX led to parallel advances that thereby raised the important issue as to whether therapy with one drug influences the efficacy and the safety of the other. We have previously shown that the benefit of clopidogrel in the CLARITY-TIMI 28 trial was comparable regardless of whether it was given with UFH or LMWH (4). We also observed that patients treated with LMWH (predominantly ENOX) had a lower rate of cardiovascular death or MI compared with patients treated with UFH, even among patients who were randomized to clopidogrel (13). However, treatment with the two heparins was not randomized in the CLARITY-TIMI 28 trial, and although we adjusted for propensity to receive LMWH, residual confounding could not be excluded. We now build upon these observations by demonstrating that randomization to treatment with ENOX results in a comparable reduction in the composite of death or ischemic complications even among patients who were also treated with clopidogrel. In addition, we found that the use of ENOX in patients who also received a fibrinolytic, aspirin, and clopidogrel was not associated with a statistically significantly higher rate of bleeding or ICH than was seen when used in patients not treated with clopidogrel. Nonetheless, the rate of major bleeding was numerically greatest in patients who received both ENOX and clopidogrel. Therefore, the decision to administer a fibrinolytic, dual antiplatelet therapy, and ENOX should take into account an individual patient's risk of bleeding. Overall, patients receiving clopidogrel tended to have a slightly larger absolute reduction in ischemic events but also a slightly greater absolute excess in bleeding with ENOX versus UFH, compared with patients who were not receiving clopidogrel. Thus, the net clinical benefit of

Table 5 Net Clinical Benefit Through 30 Days

Outcome	Clopidogrel Use	ENOX	UFH	Absolute Risk Reduction (95% CI)	$p_{interaction}$
Death, MI, myocardial ischemia, stroke, or major bleeding	Yes	131/1,083 (12.1)	158/1,090 (14.5)	2.4% (−0.5, 5.3%)	0.61
	No	910/6,528 (13.9)	1,002/6,390 (15.7)	1.7% (0.5, 3.0%)	

Data are presented as n/N (%).
RR = risk ratio for event in patients randomized to enoxaparin versus unfractionated heparin; other abbreviations as in Tables 1, 2, and 3.

ENOX over UFH was quite similar in patients who were and were not receiving clopidogrel.

The rates of adverse cardiovascular events in the ExTRACT-TIMI 25 trial were lowest in patients who received both clopidogrel and ENOX. This phenomenon was also observed in the CLARITY-TIMI 28 trial (13). However, such data must be interpreted with great caution, because allocation to only 1 of the 2 drugs was randomized in each trial. Nonetheless, in each trial the benefit of the randomized treatment was consistent regardless of the use of the other adjuvant therapy. Thus, it seems likely that the combined use of both clopidogrel and ENOX will yield additive benefits for patients being treated with fibrinolytic therapy for STEMI.

Study limitations. Potential limitations of this study merit consideration. Use of clopidogrel was not randomized but rather at the discretion of the treating physician and thus could have been influenced by patient or physician factors. For that reason, our analyses focused on the comparison of patients treated with ENOX versus UFH, allocation to which was randomized, and thus such comparisons should be free of confounding. Furthermore, even though no significant imbalances of baseline characteristics were observed between the ENOX and UFH arms within the clopidogrel and no clopidogrel cohorts, we adjusted for components of the TIMI risk score for STEMI to minimize any confounding. The doses and exact times of clopidogrel administration were not recorded. However, whether the clopidogrel was given during administration of study medication was noted. Therefore, to focus exclusively on medical therapy for STEMI, we excluded patients who underwent PCI (who would routinely be treated with clopidogrel after their procedure) and only included in the clopidogrel cohort patients who received clopidogrel during study drug administration. The dose of ENOX in the ExTRACT-TIMI 25 trial was modified on the basis of age and renal function. Moreover, the ExTRACT-TIMI 25 trial excluded men with a serum creatinine >2.5 mg/dl and women with a serum creatinine >2.0 mg/dl. Thus, we cannot comment on the efficacy and safety of ENOX in combination with clopidogrel without dose-adjustment of ENOX for age and in patients with severe renal insufficiency. Furthermore, the ExTRACT-TIMI 25 trial was a comparison of a strategy of ENOX given throughout the index hospital stay versus UFH given for at least 48 h. Thus, any differences in outcomes between the 2 strategies might reflect differences in the type of anticoagulant, the duration of treatment, and the likelihood of rebound after discontinuation. We found no statistically significant interactions in terms of the efficacy or safety profile of ENOX compared with UFH. Although the number of patients analyzed in the clopidogrel (n = 2,173) and no clopidogrel (n = 12,918) subgroups were relatively large, we cannot exclude the possibility of modest degrees of effect modification remaining undetected, especially for uncommon events such as bleeding and ICH. A very large 2 × 2 factorial design trial would be the optimal means by which to formally evaluate the encouraging signal we have observed for the additive benefits of combination therapy.

Clinical implications. We found that in patients with STEMI treated with fibrinolytic therapy and aspirin, ENOX significantly and comparably reduced the rate of MACE, both in patients who were and were not treated with clopidogrel. The absolute excess of TIMI major bleeding seen with ENOX over UFH was numerically but not significantly greater in patients who were treated with clopidogrel compared with those who were not, and there was no significant excess in intracranial hemorrhage regardless of clopidogrel use. The net clinical benefit of ENOX over UFH was quite similar in patients, irrespective of concomitant treatment with clopidogrel. Viewing the totality of data, the CLARITY-TIMI 28 trial (4), the COMMIT/CCS-2 trial (5), and now the ExTRACT-TIMI 25 trial suggest that the combination of a fibrinolytic, aspirin, clopidogrel, and ENOX offers an attractive pharmacologic reperfusion strategy for patients presenting with STEMI.

Reprint requests and correspondence: Dr. Elliott M. Antman, TIMI Study Group, 350 Longwood Avenue, Boston, Massachusetts 02115. E-mail: eantman@rics.bwh.harvard.edu.

REFERENCES

1. Antman EM, Anbe DT, Armstrong PW, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1999 Guidelines for the Management of Patients With Acute Myocardial Infarction). Circulation 2004;110:e82–292.
2. Antman EM. The search for replacements for unfractionated heparin. Circulation 2001;103:2310–4.
3. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin with fibrinolysis for ST-elevation myocardial infarction. N Engl J Med 2006;354:1477–88.

4. Sabatine MS, Cannon CP, Gibson CM, et al. Addition of clopidogrel to aspirin and fibrinolytic therapy for myocardial infarction with ST-segment elevation. N Engl J Med 2005;352:1179–89.
5. Chen ZM, Jiang LX, Chen YP, et al. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. Lancet 2005;366:1607–21.
6. Antman EM, Morrow DA, McCabe CH, et al. Enoxaparin versus unfractionated heparin as antithrombin therapy in patients receiving fibrinolysis for ST elevation MI: design and rationale for the Enoxaparin and Thrombolysis Reperfusion for Acute Myocardial Infarction Treatment Thrombolysis in Myocardial Infarction-Study 25 (ExTRACT-TIMI 25). Am Heart J 2005;149:217–26.
7. Bovill EG, Terrin ML, Stump DC, et al. Hemorrhagic events during therapy with recombinant tissue-type plasminogen activator, heparin, and aspirin for acute myocardial infarction. Results of the Thrombolysis in Myocardial Infarction (TIMI), Phase II trial. Ann Intern Med 1991;115:256–65.
8. Morrow DA, Antman EM, Charlesworth A, et al. TIMI risk score for ST-elevation myocardial infarction: a convenient, bedside, clinical score for risk assessment at presentation: an Intravenous NPA for Treatment of Infarcting Myocardium Early II trial substudy. Circulation 2000;102:2031–7.
9. The TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932–6.
10. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Randomised trial of intravenous streptokinase, oral aspirin, both or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. Lancet 1988;ii:349–60.
11. The GUSTO Investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. N Engl J Med 1993;329:673–82.
12. Eikelboom JW, Quinlan DJ, Mehta SR, Turpie AG, Menown IB, Yusuf S. Unfractionated and low-molecular-weight heparin as adjuncts to thrombolysis in aspirin-treated patients with ST-elevation acute myocardial infarction: a meta-analysis of the randomized trials. Circulation 2005;112:3855–67.
13. Sabatine MS, Morrow DA, Montalescot G, et al. Angiographic and clinical outcomes in patients receiving low-molecular-weight heparin versus unfractionated heparin in ST-elevation myocardial infarction treated with fibrinolytics in the CLARITY-TIMI 28 trial. Circulation 2005;112:3846–54.